A Long-Term Follow-up Study of Asthmatic Children Discontinued Allergen-Specific Immunotherapy

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J Child Sci 2024;14:e19–e23.

Abstract

Our objective was to explore the factors associated with the prognosis of allergic asthmatic children with poor compliance with subcutaneous immunotherapy (SCIT). A telephonic follow-up was conducted in 616 asthmatic children who received SCIT treatment from June 2005 to October 2010. The status of asthmatic controlled was based on their level of asthma symptom control when they were followed-up. Seven factors, including sex, age, family history of allergic disease, severity of mite allergy, times of SCIT, whether inhaled corticosteroids regularly, and with rhinitis or not, were analyzed. In total, 322 asthmatic children discontinued the 3-year course of SCIT. Of the 127 children included in the final analysis, 85 (66.9%) were asthmatic controlled patients and 42 (33.1%) were asthmatic uncontrolled patients. The median (interquartile range) age of the 127 asthmatic children was 7.1 ± 4.8 years. The proportion of male and female was 87/40. In the seven factors, family history of allergic diseases ($p = 0.035$), whether inhaling corticosteroids regularly ($p = 0.007$), were significantly related to the level of asthma symptom control, whereas the age of these asthmatic children, severity of mite allergy, times of SCIT, and asthma with rhinitis or not had no relation to the level of asthma symptom control. Our findings revealed that the family history of allergic diseases was an important factor affecting the prognosis of childhood asthma, and inhaling corticosteroids regularly after discontinuing SCIT could significantly improve their prognosis. These results could provide value in clinical asthma treatment.

Keywords
- asthma
- subcutaneous immunotherapy
- compliance
- follow-up
- risk factors

Introduction

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is characterized by variable symptoms of wheeze, shortness of breath, chest tightness, and/or cough and by variable expiratory airflow limitation. The global prevalence of asthma ranges from 1 to 22% of the population in different countries.[1] Allergic asthma often commences in childhood and is associated with a past and/or family history of allergic disease such as eczema and allergic rhinitis. Allergens, especially house dust mites (HDMs), are the main environmental risk factors for developing asthma in children. Although these asthmatic children have accepted first-line treatment, such as inhaled

received
August 17, 2023
accepted after revision
November 19, 2023

DOI https://doi.org/10.1055/s-0044-1787681.
ISSN 2474-5871.

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

corticosteroids, leukotriene modifiers, long-acting β2-agonists, and short-acting β2-agonists as needed, some children still need additional treatment to improve asthma control.[2,3]

Allergen-specific immunotherapy (AIT) is the only disease-modifying treatment for patients with immunoglobulin E (IgE)-mediated allergy due to airborne allergens. Subcutaneous immunotherapy (SCIT) has been the accepted effective AIT for allergic rhinitis and asthma over several years.[4] The clinical effectiveness of AIT requires the administration of standardized allergen extracts in adequate doses and for sufficient period of time (3–5 years).[4] However, a part of these asthmatic children discontinued SCIT because of no efficacy in short time, expensive fees, complex process of the treatment, and adverse reactions.[5,6] Poor compliance is a considerable problem of AIT. Therefore, further study is needed to investigate the key factors that influence the prognosis of allergic asthmatic children with poor compliance with SCIT.

In our study, we aimed to explore the key risk factors affecting the level of asthma symptom control over a long period of follow-up in allergic asthma children who did not complete the 3-year course of SCIT treatment, thereby providing valuable information for effective treatment and scientific management of such allergic asthma children.

Methods

Patients

A total of 616 children diagnosed with allergic asthma who underwent SCIT from June 2005 to October 2010 at the Department of Respiratory Disease of Children's Hospital of Chongqing Medical University were potentially enrolled, and 322 of them discontinued SCIT. A telephonic follow-up was conducted in those children who received SCIT but did not finish the 3-year course. In total, 127 of the 322 children completed the telephonic follow-up and were included in the final analysis. These asthmatic children were divided into two groups (the controlled and the uncontrolled groups) based on their level of asthma symptom control. Of 127 children, 85 (66.9%) got asthma controlled, whereas 42 (33.1%) did not (►**Fig. 1**).

The study was approved by the ethics committee of Dazhou Central Hospital (Ethical Application Ref: IRB00000 0006-17006), and the need for informed consent from participants in this study was waived.

Skin Prick Test

Skin prick test (SPT) is used to detect systemic sensitization to airborne and food allergens and is used as the first-line diagnostic approach worldwide.[7] The test requires that a minimal amount of an allergen extract containing specific components, both genuine and cross-reacting, along with the appropriate negative (normal saline) and positive (1 mg/mL histamine) control, to be put into contact with dermal mast cell by pricking the epidermis. No patients had taken antihistamines of any type or any other medication that could influence the result of SPT for 7 days before the prick test. Wheal size was measured in millimeters in two perpendicular directions at 20 minutes after the initial prick. Only wheals of the extract at least 3 mm in diameter larger than the negative control were regarded positive. The severity of allergen sensitization depends on the value that

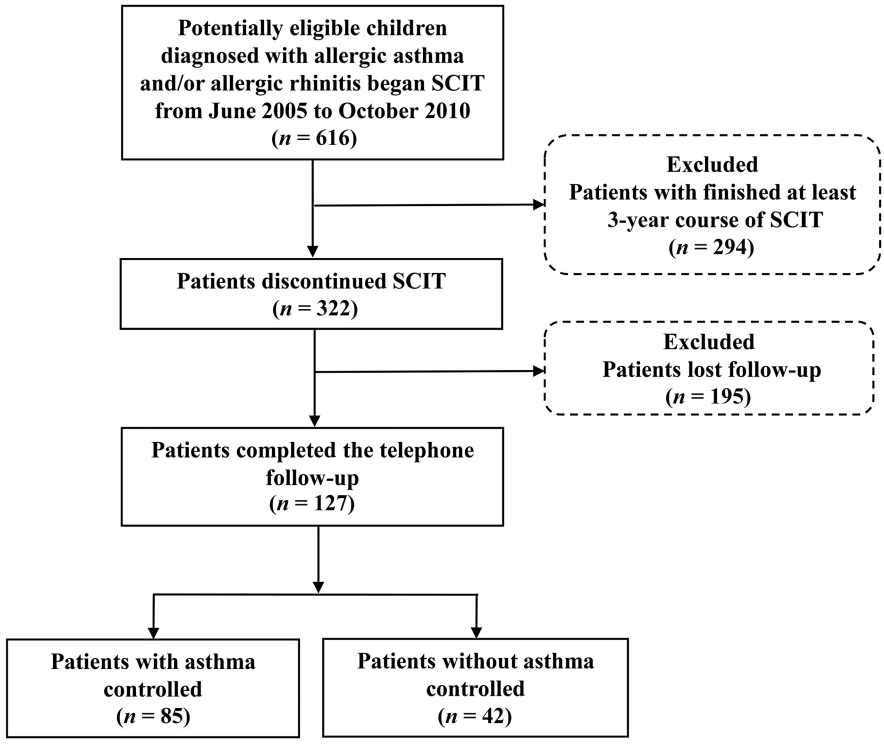

Fig. 1 Enrollment of patients in this study. Abbreviations: SCIT, subcutaneous immunotherapy.

deprived from size of allergen dividing by size of histamine. In our study, allergic sensitization was confirmed based on the SPT using standardized extracts (ALK-ABELLO, Denmark). We obtained this information from the electronic system for the management of these children.

Subcutaneous Allergen Immunotherapy

In this study, commercial standardized dust mite extracts (ALK-ABELLO, Denmark) were administered according to the manufacture's recommendations for both the initial and maintenance phase. In different phases, the concentration of the extracts and the interval time between the two administrations were different (►**Supplementary Table S1**, available in the online version).

Level of Asthma Symptom Control

The level of asthma symptom control is the extent to which the manifestation of asthma can be observed in the patient or has been reduced or removed by treatment. In our study, the symptom control included frequency of asthma symptoms (days per week), any night waking due to asthma or limitation of activity, and frequency of reliever use for relief of symptoms according to the Global Initiative for Asthma Report (GINA; ►**Supplementary Table S2**, available in the online version).

Statistical Analysis

All statistical analysis was performed using the Statistical Package for Social Sciences (SPSS version 21, IBM Crop). The Pearson chi-square test was used to determine the association between categorical variables, and the Mann–Whitney test was used for continuous variables.

Results

Characteristics of the 127 Children who Discontinued Subcutaneous Allergen Immunotherapy

The clinical data were summarized in ►**Table 1**. Among 127 children retained in the study, the median age at SCIT start was 7.1 ± 4.8 years, and most children (87/129, 68.5%) were male. According to the assessment of asthma symptom control, we divided the 127 children into two groups: controlled group (85/127 66.9%) and uncontrolled group (42/127, 33.1%, including 35 cases in partly controlled and 7 cases in uncontrolled). Twenty-seven (21.2%) suffered from both allergic asthma and allergic rhinitis. Forty five (35.4%) had a family history of allergic disease, such as eczema, allergic rhinitis, allergic asthma, or food or drug allergy. In 127 children, 53 (41.7%) discontinued SCIT due to no effect in short time, 29 (22.8%) for remission of asthma, 45 (35.5%) for other reasons, such as expensive fees, complex process of treatment, adverse reaction, long distance from the hospital, and without enough time for treatment. Twenty-one (16.5%) had side-effects of SCIT. After discontinuing SCIT, 71 (55.9%) inhaled corticosteroids regularly, 23 (18.1%) inhaled corticosteroids irregularly, and 33 (26.0%) did not inhaled corticosteroids (►**Table 1**).

Table 1 Basic information of asthmatic children

Characteristics	Frequency (%) ($n = 127$)
Age, median (IQR)	7.1 (4.8)
Sex, male	87 (68.5)
Family history of allergic disease	45 (35.4)
Accompanied with allergic rhinitis	27 (21.2)
Side-effects of SCIT	21 (16.5)
Reasons of discontinued SCIT	
Remission of asthma	29 (22.8)
Poor efficacy	53 (41.7)
Others[a]	45 (35.5)
ICS	
Regularly	71 (55.9)
Irregularly	23 (18.1)
No	33 (26.0)
Level of asthma symptom control	
Well controlled	85 (66.9)
Poorly controlled	42 (33.1)

Abbreviations: ICS, inhaled corticosteroids; IQR, interquartile range; SCIT, subcutaneous specific immunotherapy.
[a]Others including expensive fees, complex process of SCIT, adverse reaction, long distance from hospital, and having no time for treatment.

Comparison of Clinical Characteristics among the Controlled Group and Uncontrolled Group

We compared the clinical characteristics of the controlled group and the uncontrolled group (►**Table 2**). There was no significant difference in age, severity of allergen sensitization, and times of SCIT received. No significant difference was observed in sex and whether accompanied by side-effects of SCIT and allergic rhinitis. The severity of HDMs and tropic mites sensitization did not show a significant difference between the controlled group and the uncontrolled group. The proportion of family history of allergic disease in the controlled group was significantly lower than that of the uncontrolled group ($p = 0.035$). And the proportion of inhaling corticosteroids regularly in the controlled group was higher than that of the uncontrolled group ($p = 0.007$).

Discussion

AIT is an effective therapy that can improve allergic response by modifying the underlying disease, and HDM AIT has been incorporated in the GINA recommendations as an add-on treatment for HDM allergic asthma 2020.[1] At least 3 years of treatment is required to obtain the long-term benefits and disease-modifying effects of AIT.[4] A previous study found that 85% of allergic asthmatic children had controlled asthma after 3-year course of SCIT.[8] As another study reported, for the 46 patients who completed SCIT, 44 (95.7%) had controlled asthma and 2 (4.3%) had uncontrolled asthma, and the cumulative incidence rates of remission from adult

Table 2 Comparison of clinical characteristics between the controlled and uncontrolled patients

Characteristics	Controlled ($n = 85$)	Uncontrolled ($n = 42$)	*p*-Value
Age (median ± IQR)	7.7 ± 5.4	7.4 ± 6.6	0.64
Severity of allergen (median ± IQR)			
Dust mites	0.99 ± 1.47	0.98 ± 0.95	0.86
House dust mites	1.12 ± 0.89	1.36 ± 0.95	0.17
Tropical mites	0.19 ± 0.49	0.37 ± 0.59	0.21
Times of SCIT received	23.8 ± 13.4	21.7 ± 12.3	0.33
Sex			
Male	59 (46.5%)	28 (22.0%)	0.84
Female	26 (20.5%)	14 (11.0)	
Family history of allergic disease			
Yes	16 (12.6%)	6 (4.7%)	0.035[a]
No	69 (54.3%)	36 (28.4%)	
Accompanied with allergic rhinitis			
Yes	22 (17.3%)	5 (3.9%)	0.054
No	63 (49.6%)	37 (29.2%)	
Side-effects of SCIT			
Yes	13 (10.2%)	6 (4.7%)	0.582
No	72 (56.7%)	36 (28.4%)	
ICS			
Regularly	52 (41.0%)	19 (15.0%)	0.007[b]
Irregularly	9 (7.1%)	14 (11.0%)	
No	20 (15.7%)	13 (10.2%)	

Abbreviations: ICS, inhaled corticosteroids; IQR, interquartile range; SCIT, subcutaneous specific immunotherapy.
Note: [a]$p < 0.05$; [b]$p < 0.01$.

asthma were 86.9% upon treatment with SCIT for more than 3 years.[9] Despite the clinical value of AIT, adherence to SCIT is far from being optimal. In our previous study, 52.2% (322/616) of children who were diagnosed with asthma received but discontinued SCIT because of no efficacy in short time, expensive fees, complex process of the treatment, and adverse reaction.[6] Similarly, studies indicated that the SCIT adherence at 3 year were only 58.7 to 64.6%.[5,10] For children who did not complete 3 to 5 years course of SCIT, whether the effect is related to the times or the duration of SCIT, few study has demonstrated this problem. In our study, among the 127 children who discontinued 3-year course of SCIT treatment, only 66.9% got well and asthma symptom resolved. And there was no significant difference in times of SCIT received between the controlled group and the uncontrolled group. Researchers have not yet agreed upon the optimum period for administering immunotherapy.

In general, atopic sensitization is defined when allergen-specific serum IgE E (sIgE) are detected or a positive SPT to extracts made from whole allergen sources, often using arbitrary cut-off points of sIgE > 0.35 ku/L, or a mean wheal diameter >3 mm.[11] These standard allergy tests have high sensitivity, but in themselves do not signify disease. There is a difference between allergic asthma with asthma symptoms induced by a defined allergen exposure, and asthma in a subject characterized as "sensitized" with no relation between allergen exposure and clinical reaction. Elevated serum-specific IgE levels or a positive SPT and symptoms on exposure to the sensitizing allergen are currently the sole standard for allergy diagnosis and inclusion criteria for starting AIT. In the study of Lee et al, initial sIgE level to HDM did not show a significant difference between remission and nonremission groups after adjusting demographic variables.[9] A preliminary retrospective study pointed that children with high sIgE perceived AIT efficacy, whereas children with low sIgE perceived slight AIT benefit.[12] Sly et al have revealed that quantification of atopic sensitization in early life among young children is one of the best discriminations to identify those who are at high risk of subsequent development of persistent asthma.[13] The severity of HDMs and tropic mites sensitization did not show a significant difference between the controlled group and the uncontrolled group in our study. More data are needed to assess the relationship between the levels of sIgE and the efficacy of AIT.

Regular daily low-dose inhaled corticosteroids are recommended as the preferred initial treatment for controlling asthma in children in the GINA guidelines.[1] Adherence to long-term inhaled corticosteroids is optimal among patients with asthma and critical in preventing asthma exacerbation.[14,15] However, suboptimal compliance with inhaled corticosteroids therapy remains a major obstacle in pediatric asthma management. In the study of Zheng et al, the noncompliance group with discontinued inhaled corticosteroids had an effect on lung function, including a decrease in forced expiratory volume in 1 second (FEV1), ratio of FEV1 to forced vital capacity, peak expiratory flow.[1] In the European Academy of Allergy and Clinical Immunology guidelines, HDM SCIT is recommended as an add-on to regular asthma therapy for adults and children with controlled or partially controlled HDM-driven allergic asthma.[4] Hence, AIT cannot replace inhaled corticosteroids in the therapy of asthma. In our study, the proportion of inhaling corticosteroids regularly in the well-controlled group was significantly higher than that of the uncontrolled group. These results suggested that continue inhaled corticosteroids regularly in the children who discontinued 3-year course of SCIT was important for patients for asthma control.

Family history of asthma and other allergic diseases have been linked to the risk of childhood asthma previously.[16,17] As suggested in research,[18] children with a family history of asthma may have more frequent uncontrolled asthma due to increased asthma severity. Another reason for this result is the parents with asthma may be less concerned about the asthma symptoms of their child as they are familiar with asthma symptoms themselves. But Roorda et al have reported that a positive family history of asthma or atopy,

as well as associated allergic disease in the child did not predict the prognosis of childhood asthma throughout life.[19] There are different views on the effect of family history of asthma on the prognosis of children with asthma. In our study, we found that the proportion of family history of allergic disease in the well-controlled group was notably lower than that of the uncontrolled group. Together, our result suggested that the family history of allergic disease may affect the prognosis of childhood allergic asthma who did not complete 3-year course SCIT treatment. The result reinforced that the parents should have close observation and use scientifical medicine for such children with a family history of asthma to prevent treatment failures and asthma exacerbations.

Our study has some limitations that need to be acknowledged. First, the sample size was relatively small. Second, it was a retrospective design single-center study, which may make the results less generalizable. Thus, large-scale prospective multicenter cohorts are required. Furthermore, additional studies need to be conducted to explore the underlying mechanism for the risk factors and uncontrolled asthma. Despite these limitations, our long period of follow-up study highlighted valuable risk factors affecting the level of asthma symptom control in allergic asthma children who did not complete the 3-year course of SCIT treatment, which recommended that those patients require closer monitoring and creating patient awareness toward their condition.

Conclusion

The finding of the study indicated that family history of allergic diseases, whether inhaling corticosteroids regularly, is an important factor affecting the prognosis of asthma in allergic asthma children who did not complete the 3-year course of SCIT treatment. These findings have important clinical implications. The present findings of potential risks for asthma control can help clinicians identify patients who are more likely to develop asthma control failure in the above patients and who may therefore require closer monitoring and creating patient awareness toward their condition including encouraging attention to these factors and the appropriate use of their medications.

Authors' Contributions

Y.H. and B.Z. conceived and designed the experiments, performed the data analysis, prepared figures and/or tables, and authored or reviewed drafts of the paper. Y.H. collected data and analyzed the data. J.L. authored or reviewed drafts of the paper. All authors approved the final draft. We have no conflict of interest.

Funding

This study was supported by the scientific fund of Health Commission of Sichuan Province (18PJ040) and Sichuan University-Dazhou Municipal People's Government Strategic Cooperation Special Fund Project (2020CDDZ-23).

Conflict of Interests

None declared.

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